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INTRALEUKOCYTIC BODIES IN SCARLET FEVER.*

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Since Döhle's first article on "Leukocytic Inclusions in Scarlet Fever," a number of workers have investigated the occurrence, significance, and nature of such inclusions but the conclusions derived from these investigations differ very much.

Döhle[1] examined smears of blood fixed by alcohol from 30 cases of scarlet fever and from numerous other diseases, which he does not specify. The smears were stained either with a mixture of Hoppe-Seyler's reagent, water and Michaelis' azure blue, or with an acid solution of orseiles mixed with acid hematoxylin. He also used Pappenheim's stain. By these methods he observed inclusions in the cytoplasm of nearly all neutrophiles almost invariably in scarlet fever. These bodies stained blue with the two first-mentioned stains, and took a pale red with Pappenheim's mixture. Their size and shape varied greatly, some being as large as one-sixth the size of the nucleus, and round or rod-shaped, or oval with one pointed end. The number of bodies per cell varied from one to six. The only cases of scarlet fever in which such bodies did not occur were two examined late in the disease. Only in cases of two other diseases were similar bodies found; viz., two cases of carcinoma and one of pneumonia, in which there was a history of syphilis (the author stating that in this particular instance his slides might have become mixed with those of scarlet fever). Döhle holds that because the bodies stain red with Pappenheim's stain they need not be confused with nuclear fragments; he also finds similar bodies free in the blood.

In a more recent article Döhle[2] describes spiral forms in the cytoplasm of leukocytes, and also in the blood of two cases of scarlet fever. These he believes are spirochaetes and he names them *Spirochaeta scarlatinae*. The bodies which he described in the leukocytes he holds to be fragments of the parasites of both diagnostic and prognostic significance.

Stimulated by Döhle's work, Kretschmer[3] studied some 30 cases of scarlet fever and about 70 controls. At first he used Döhle's method, but soon changed to fixation by methyl alcohol and staining with Manson's stain, because this technic is equally efficient and much simpler. He also tried Giemsa's stain. Kretschmer verified Döhle's results in regard to scarlet fever, finding bodies in all early cases; they usually disappeared by the 8th–10th day, occasionally somewhat later. Döhle and Kretschmer both failed to find such bodies in animals; the latter failed to find any relation between the temperature and the occurrence of the bodies. The other diseases in which he found the bodies, but by no means constantly, were diphtheria, tuberculosis, and pneumonia. They were not found in leukocytes from normal persons or in cases of measles.

Nicoll and Williams[4] used Kretschmer's technic, and also Giemsa's stain over night. In 51 cases of scarlet fever in which the patients had been sick more than eight days the bodies were present in all except six cases. Bodies were also found

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[1] *Centralbl. f. Bakt.*, I, Orig., 1912, 61, p. 63.

[2] *Centralbl. f. Bakt.*, I, Orig., 1912, 65, p. 57.

[3] *Berl. klin. Wchnschr.*, 1912, 49, p. 499.

[4] *Arch. Ped.*, 1912, 29, p. 350.

in one of 12 cases of measles—a doubtful case—and in one case of erysipelas and one of pneumonia. Nicoll and Williams believe strongly in the diagnostic value of the bodies. In another article, Nicoll[1] reports the results of the study of 115 cases of scarlet fever; in 16 only were the bodies not found. One of the patients had been sick four days and the diagnosis was questionable, two had been sick five days, and the remainder were sick for a longer period. He found them also in erysipelas, typhoid fever, and sepsis.

Ahmed[2] does not regard the bodies as peculiar to scarlet fever because he finds them in tuberculosis, erysipelas, and measles. He holds that they have some relation to fever and that they may be nuclear fragments or degenerated cytoplasm.

Kolmer's[3] results in 216 cases of scarlet fever agree with those of Döhle and others. He found them in the majority of 50 cases of diphtheria, in erysipelas, sepsis, pneumonia, and empyema. He failed to find them in measles (12 cases) and in a number of other diseases including varicella, pelvic diseases, pericarditis, goiter, furunculosis, eczema, gonorrhea, bronchopneumonia, German measles, mastoiditis, gastroenteritis leukemia, and pernicious anemia. Kolmer concludes that the occurrence of the bodies is connected with streptococcal infections, and that they are of value in differentiating scarlet fever from rötheln, measles, and gastrointestinal rashes. He believes them to be derived from the cytoplasm of the cells.

The results obtained so far may be summarized as follows: It is agreed that certain bodies are present in the leukocytes in the early stages of scarlet fever, which are not found in normal blood; but authorities differ as to their occurrence in other diseases, as to their diagnostic significance, and as to their nature.

In the study now reported the blood was drawn from the lobe of the ear, smears made and fixed with methyl alcohol. Smears were also fixed by formalin, heat, alcohol, and ether, for the purpose of comparison. Manson's stain was used for the most part, but methylene blue, Delafield's hematoxylin, Leishman's stain, Pappenheim's stain, and carbol-thionin were also used. Cases of scarlet fever, erysipelas, and measles were studied each day for a longer or shorter time after their entrance into the hospital, and in each instance at least 100 neutrophiles were examined. Twenty-five cases of scarlet fever were examined. In six of these the result was practically negative, that is, very few leukocytes with bodies in their interiors were found. In one of the negative cases the illness which was exceptionally mild had lasted only five days; in the others the examinations were made after the febrile stage had passed. In the other 17 cases there was no difficulty in finding the bodies. In one case 68 per cent of the neutrophiles contained the bodies; in most of the others the percentage ran between 25 to 40. In making the counts only cells containing definite and distinct bodies were counted as positive. By daily examination, it soon became apparent that the percentage of leukocytes with bodies varied from day to day, and that there are fairly constant relationships in each case in this respect. Thus the highest counts were found on the fifth day in most cases, the average being slightly lower on the fourth day. Chart 1, which illustrates this point, shows that the leukocytes with inclusions increased in number until the fifth day and then gradually diminished, none being found on the ninth day. In most cases of scarlet fever the leukocytes became practically free from bodies between the seventh and 10th days of the disease. The bodies were found to be most numerous when the clinical symptoms were most marked. As shown in Chart 2, the temperature curve corresponds quite closely to that of the leukocytes

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[1] *Arch. Ped.*, 1912, 29, p. 416.

[2] *Berl. klin. Wchnschr.*, 1912, 46, p. 1232.

[3] *Amer. Jour. Dis. of Child.*, 1912, 4, p. 1.

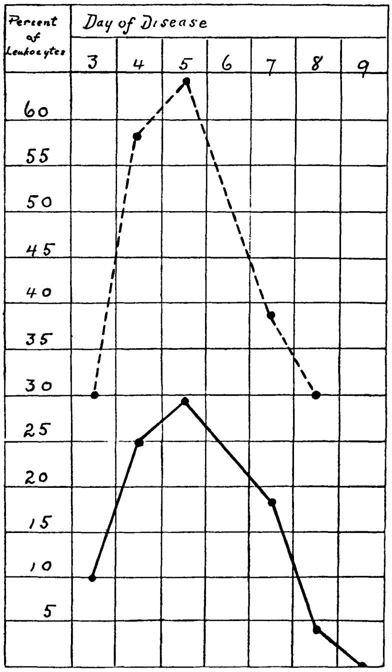

Chart 1.—Percentage of leukocytes containing free bodies and those containing fragments attached to nuclei, in a case of scarlet fever.

——— =leukocytes with free bodies.
- - - - - =leukocytes with attached fragments.

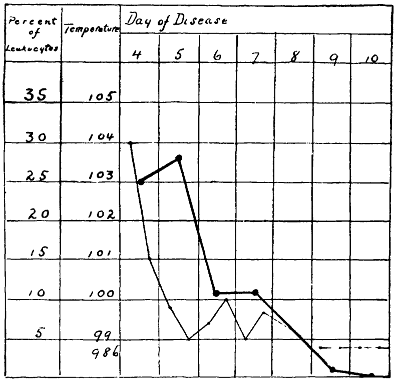

Chart 2.—The relation of free bodies in leukocytes to temperature, in a case of scarlet fever.

——— =leukocytes with free bodies.
——— =temperature.

with inclusions, anticipating the latter by about a day. When the temperature becomes normal the inclusions practically always disappear in from 24 to 48 hours, and when fever again reappears the bodies also return.

Seven cases of measles were examined, two being afebrile at the time, and in one of these 10 per cent, and in the other 3 per cent of the leukocytes contained bodies. In the other five cases from 10 to 24 per cent of the leukocytes were positive, the highest percentage being obtained in the case of a child with hemorrhagic measles with high temperature (see Fig. 1).

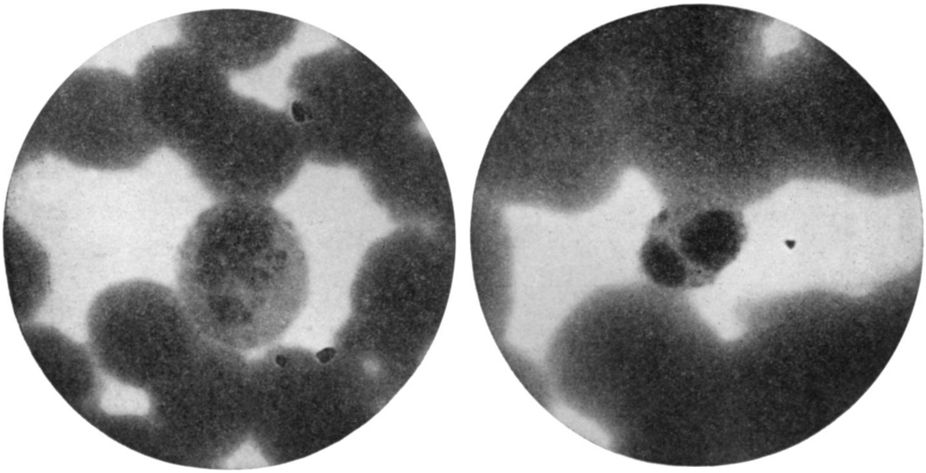

FIG. 1.—Intraleukocytic bodies in measles. × 1000.

The same relation between the intraleukocytic bodies and fever was also found in erysipelas of which five cases were studied. Two of these were afebrile and practically free from bodies. The highest percentage in erysipelas was 60. This occurred in the case of an old man on the day on which his temperature was 104°.

In all these cases the leukocytes showed partially detached nuclear fragments similar in general outline to the free bodies, and also irregular projections or stumps from the nuclei, as if fragments had been torn off. Indistinct spiral bodies similar to those described by Döhle as *Spirochaeta scarlatinae* were found in measles and erysipelas as well as in scarlet fever.

The other cases examined may be divided into febrile, and afebrile.

All of the fever cases studied gave positive results; viz., two cases of diphtheria, two of fever due to antitoxin, two of gastro-intestinal fever, two of empyema, a case each of brain tumor and of neuritis, two cases of malaria, two of tuberculosis, and four cases of typhoid fever.

In four normal individuals examination of 100 cells in each person showed that from 2 to 4 per cent of the leukocytes contained bodies similar to those in scarlet fever. When the blood was subjected to a vigorous shaking in citrate solution, and afterward washed, the number of bodies was greatly increased so that the percentages rose to from 12 to 20, and at the same time the number of leukocytes with irregular nuclear projections were increased proportionately.

Bodies were also found in the leukocytes in three cases of local suppuration without fever, in a case of myelogenous leukemia, and a case of rickets.

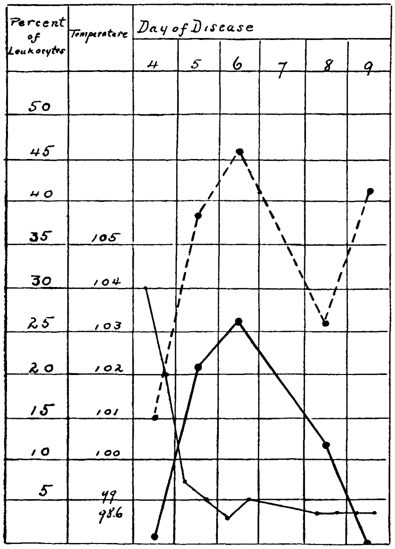

CHART 3.—The relation between percentages of leukocytes containing bodies, and those containing fragments attached to nuclei, in a case of measles.

——— =leukocytes with free bodies.
- - - - - =leukocytes with attached fragments.
——— =temperature.

In attempting to arrive at some conclusion in regard to the nature and origin of these bodies, I would suggest that their size and shape and also their reactions with staining agents indicate strongly that the majority of them are nuclear fragments. Similarly shaped bodies partially detached from the nucleus are found regularly. In scarlet fever, measles, and erysipelas the percentage of leukocytes containing partially detached fragments is a little larger than the percentage containing free bodies, both percentage curves maintaining, however, the same relation to the temperature curve (Chart 3). In fact, so far as my actual observations go, from 12 to 24 per cent of the leukocytes of blood from other sources than patients with scarlet fever, measles, and erysipelas, both in health and disease, show these attached nuclear fragments. I have stated already that by rough manipulation of normal leukocytes the number of free intraleukocytic bodies may be increased very definitely, and that at the same time there is an increase in the number of partially attached masses. The width of the pedicle may vary from that of the slenderest thread to 2μ or more. Pointed projections from the main nucleus are seen often, and suggest that fragments have been detached. Often free bodies lie in juxtaposition to such stumps. The fact that free bodies within leukocytes are colored red with Pappenheim's stain does not prove that they are not of nuclear origin, because it is well known that chromatin when separated from the nucleus soon changes in its staining reactions. Of course, it is not my intention to claim that all the bodies within the leukocytes in scarlet fever are nuclear fragments. Some may be parasites or parasitic remnants, others blood platelets, and still others of cytoplasmic nature. Many, however, and probably by far the largest number, are undoubtedly fragments split off from the nuclei of the leukocytes. This perhaps is shown most conclusively by the constant relation between the free bodies and partially attached nuclear fragments, and by the fact that both are produced by the shaking of blood. Why the number of such bodies should be increased in scarlet fever, measles, erysipelas, and probably other diseases remains unknown. As now understood, it does not seem possible that the bodies in question bear any causal relation to scarlet fever.

CONCLUSIONS.

Bodies in the leukocytes like those described by Döhle occur in many febrile diseases, and in smaller number in other diseases, and even in health. The larger part of these bodies are of nuclear origin, and may be produced by shaking the blood. It is not justifiable to regard them as having any etiologic significance.